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## EFFECT OF CHLORPROMAZINE ON ADRENAL CORTEX

BY

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# INTRODUCTION

The effects of chlorpromazine are achieved partly through a peripheral, partly through a central mechanism (9, 11). It has a universal depressant action not only on oxydative but on all cellular life (36). The peripheral action is strongly sympathicolytic and to a less degree also parasympathicolytic (12). The central action is directed especially to the reticular formation of the diencephalon. Chlorpromazine depresses its spontaneous activity and diminishes its sensitivity to afferent sensory or nociceptive impulses. It also suppresses the activating effects of peripheral sympathetic discharges at the reticular formation (1, 5, 39, 47).

Chlorpromazine has proved to be effective in protecting experimental animals against Reilly's phenomenon, the irritation syndrome caused by local irritation of sympathetic nerves, which in turn has been compared with the lesions following the alarm reaction described by Selye (14, 26, 27, 28, 37, 38, 41, 42). This effect of chlorpromazine manifests itself also as an inhibition of the hypertrophy of the adrenal cortex and other manifestations of increased corticotrophic influence (2, 3, 4, 6, 10, 17, 18). The anti-adrenaline activity of chlorpromazine cannot explain its efficiency because equally potent anti-adrenaline compounds have proved to be of little value in this respect. Also in clinical use chlorpromazine has been found effective in protecting the organism against nonspecific stress. Obviously the central effects of chlorpromazine are here of essential importance. It has been presumed that the activation of the anterior lobe of the pituitary gland after aggression were linked with the central action of adrenaline in the region of the corpora mamillaria and the posterior part of hypothalamus, which in turn control the secretion of corticotrophin. It has been suggested that chlorpromazine could depress this action of adrenaline (20, 30). This opinion is supported by clinical observations concerning the decreased corticotrophic activity of the

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pituitary gland during chlorpromazine medication (35) and the experimental finding that chlorpromazine depresses the pituitary-adrenal response to stress. (Cf. also 7.)

Chlorpromazine protects the organism against nonspecific stress expressly in small doses. In large doses it, on the contrary, may intensify the condition (22). Chlorpromazine itself has been shown to cause a fall in the adrenal ascorbic acid content indicating some release of ACTH. This effect is seen already by relatively small doses. In large doses chlorpromazine causes changes in the ascorbic acid and total cholesterol content of the adrenals similar to the effect of stress (13, 21, 34). Animal experiments have shown that chlorpromazine in prolonged use with large doses causes liver parenchyme lesions (23). It has been observed that chlorpromazine in clinical use can aggravate certain somatic illnesses (19, 31, 32, 44, 49, 50). Furtherly, in combination with electroconvulsive therapy chlorpromazine has been observed to aggravate the cardiovascular collapse caused by electro-shock. Similar reactions have been described also after chlorpromazine alone. In letal cases the post-mortem examination has revealed a condition indistinguishable from irreversible shock (16, 24, 33, 45, 51). These observations show that chlorpromazine medication itself possibly can act as non-specific stress to the organism.

The purpose of the present study is to investigate the effect of a massive chlorpromazine medication on the adrenal cortex of the white rat. In this connexion special attention is paid to the appearance of signs of stress. Therefore, notes are made of the changes in the general condition of the animals during the medication. For further evidence attention is also paid to the hemopoietic system.

# PRESENT STUDY

## MATERIAL AND METHODS

The effects of large doses of chlorpromazine were studied by 36 white male rats and 10 controls. In the beginning of medication the animals were about 100 days of age. Chlorpromazine was given subcutaneously once a day. The general condition of the animals was followed up during the medication. For this purpose the rats were weighed before and during the period of medication. 10 rats were treated with slowly increased doses (group I). On the first day the dose was 5 mg/kg body weight and the dose was increased by this same amount daily. The medication was continued until the general condition of the animals had began to weaken. At this moment, after 20 days of treatment the group was killed. 19 rats were treated with quickly increased doses. On the first day the dose was 25 mg/kg body weight and the dose was increased by this same amount daily. To 9 rats of this group an accessory daily dose of corticotrophin, 2 IU/kg body weight was given subcutaneously. The medication was continued until the animals were in a state of deep exhaustion. This was the case after 12 days of treatment with those 10 rats not receiving corticotrophin (group IIA) and after 13 days with those 9 rats receiving corticotrophin (group IIB). At this moment the animals were killed. 7 rats were treated with one single injection of 600 mg/kg body weight and the animals were killed 2 hours later (group III).

Immediately after killing the suprarenals of each animal were removed and weighed in a torsio balance, at the same time also the spleen was removed and weighed. For the study of the lipoid content of the adrenal cortex, one of the suprarenals was fixed for 24 hours in neutralized 4% formol. 10 μ frozen sections were cut and stained with the Sudan III method. Morphological study of the spleen and of the suprarenals took place after a 5-hours fixing in Zenker's solution and after staining with haematoxylin and eosin.

## RESULTS

*Changes in Body Weight and General Condition of Animals During Treatment.* — Fig. 1 shows the changes in the body weight of the animals in the groups treated with progressively increased doses of chlorpromazine. Also the doses of chlorpromazine during the course of treatment are presented in it. It can be seen that

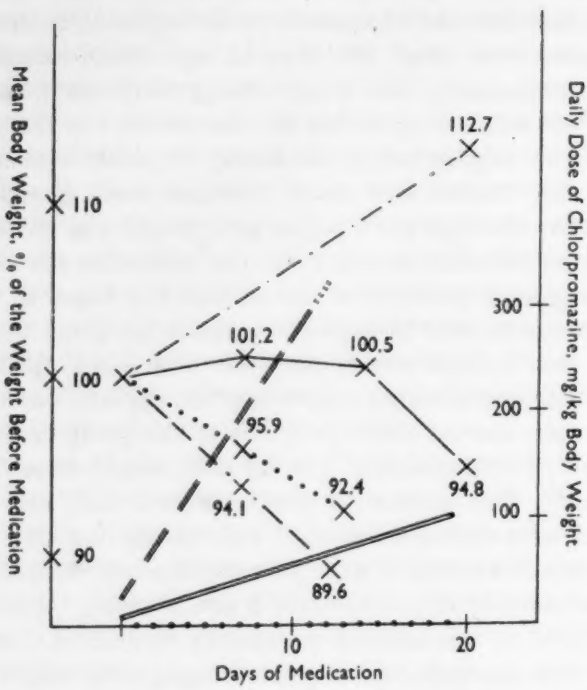



Fig. 1. — The effect of large, progressively increased doses of chlorpromazine on the mean body weight of the white male rat.

Mean body weight: ×—·—× = Control group.
×——— × = Group I, treated with slowly increased doses.
×— — — × = Group IIA, treated with rapidly increased doses.
×····· × = Group IIB, treated with rapidly increased doses and 2 IU/kg body weight of corticotrophin daily.

Daily dose of chlorpromazine:
= Group I.
= Group IIA.
= Group IIB.

in the group treated with slowly increased doses (group I) the body weight remained unchang during the first 14 days, until the daily dose of chlorpromazine had risen to 75 mg/kg body weight. After this, the body weight began to go down and until the moment of killing it had diminished by 5.2%. In accordance with this, the outlook of the rats showed no signs of depressed vitality during the first 14 days. The spontaneous activity was, however, clearly diminished and a considerable sedation could be demonstrated *e.g.* by suspending animals by their front paws from a horizontal wire. In clear contrast to control animals it often took 10—30 seconds until the rats had brought at least one hind paw up to the wire. After 14 days this sedation became progressively more evident. The animals also began to loose their interest to food and water intake, this being reflected also in the outlook of the animals. However, still at the moment of killing the animals were in a rather good general condition and the traction test described above showed no grave disturbance of the motor or equilibration ability.

In the group treated with rapidly increased doses of chlorpromazine the body weight began to decrease from the very beginning of medication. In accordance with this, a strong sedation and almost a standstill of the spontaneous motor activity was noticed. After 10 days of treatment the rats remained inert in the position in which they were placed and in the traction test they as a rule were not any more able to climb on the wire. In this stage the animals showed a tendency to spontaneous bleedings from mucous membranes, had convulsions and at the moment of killing many of them were paretic and obviously dying. The rats receiving small accessory amounts of corticotrophin (Group IIB) tolerated the medication a little better than those treated with chlorpromazine alone (Group IIA). This reflects itself also as a difference in the decrease of the body weight. In the latter group the mean decrease of the body weight was after 12 days of treatment, at the moment of killing 10.4%, in the former group the decrease was 7.6% after 13 days of medication. Nevertheless there was no essential difference between these two groups.

The group treated with one single very high dose of 600 mg/kg body weight (Group III) had 15 minutes after the injection sunk into a state of flaccid inertia, after 2 hours the respiratory

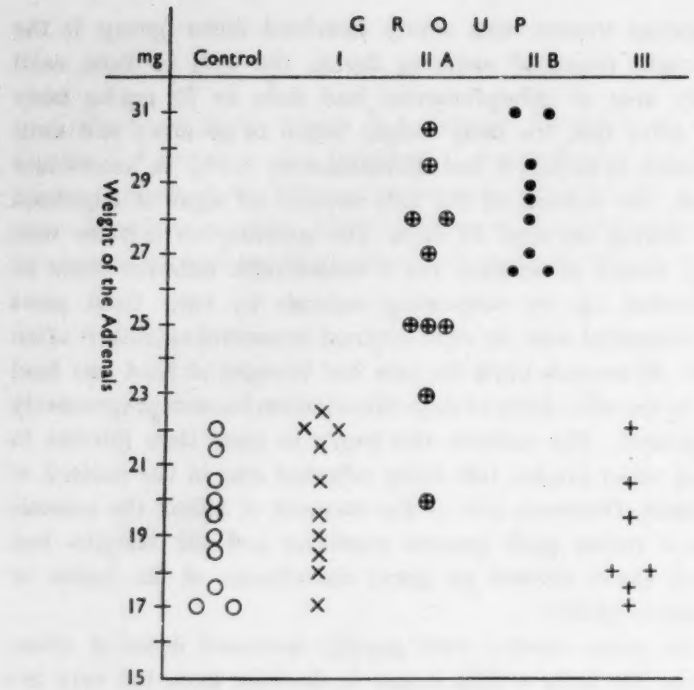



**Fig. 2. — The effect of chlorpromazine on the weight of the adrenals of the male rat. The marks indicate the mean weight of the suprarenal glands of the individual animals in different groups.**

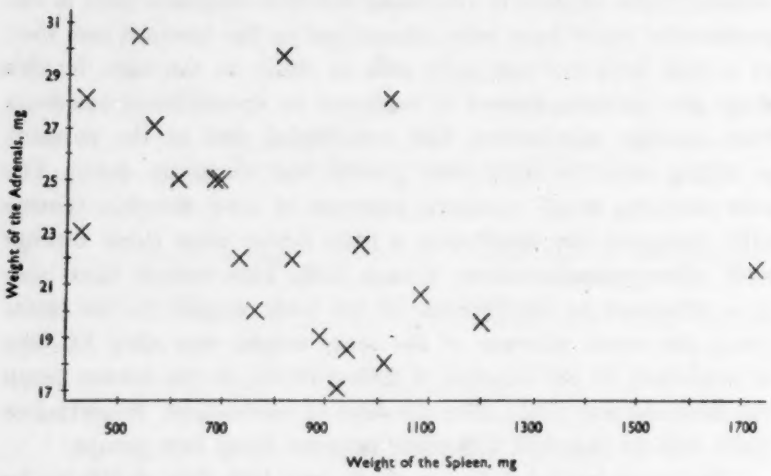



**Fig. 3. — The correlation between the weights of the adrenals and the spleen by the rats treated with progressively increased doses of chlorpromazine (groups I and IIA).**

movements had became superficial and irregular with long intervals. When this state had manifested itself, the animals were killed.

*Weights of Adrenals.* — Fig. 2 gives the weights of the suprarenals in different groups. It shows that the suprarenals have gained in weight in the groups treated with progressively increased doses of chlorpromazine. This gain in weight is not clearly seen in the group I, treated with slowly increased doses, but is prominent in the group II, treated with rapidly increased and bigger doses. The accessory application of small amounts of corticotrophin (group IIB) still intensified this gain in weight somewhat. No essential difference can, however, be seen between the groups receiving rapidly increasing doses of chlorpromazine or chlorpromazine and corticotrophin combined. The group III, treated with one single very large dose of chlorpromazine shows no difference as compared to the control group. Apparently chlorpromazine in this group has not affected the weight of the adrenals.

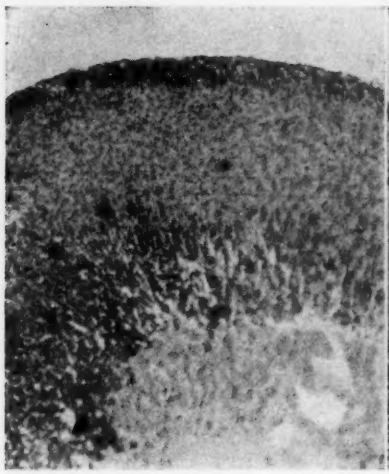
The mean weights of the suprarenals in different groups were: Group I = 20.1 mg; Group IIA = 26.1 mg; Group IIB = 28.6 mg; Group III = 18.9 mg; Control group = 19.2 mg.

*Microscopical Findings in the Adrenals.* — Sudanophilia: In the control group the cells of the glomerulosa contain numerous small Sudan-positive droplets. The transitional zone is well formed in all cases. In the cells of the fasciculata rather large Sudan-positive droplets are seen, the outer parts containing appreciably more sudanophil droplets than the inner parts. Zona reticularis is very weakly sudanophil in most cases (fig. 9). In group I sudanophilia is most clearly seen in the glomerulosa. No clear transitional zone is seen in any case. In the cells of the fasciculata plenty of Sudan-positive droplets of different size are seen, the sudanophilia diminishing gradually in the inner parts. In the cells of the reticularis only some single and very small sudanophil droplets are seen. In group IIA sudanophilia is most evident in zona glomerulosa. No transitional zone is to be seen. In zona fasciculata sudanophilia is for most part very weak, the cells containing only relatively small sudanophil droplets. Sudanophilia is gradually diminishing towards the inner parts of the fasciculata and in the cells of the reticularis only some single small Sudan-positive droplets are seen (fig. 10). In group IIB the distribution of sudanophilia is identical with that seen in group IIA (fig. 11). In group III the distribution

of sudanophilia is identical to that seen in the control group with the exception that the transitional zone is not so well formed.

Zonation: Zona glomerulosa is well formed in the control group and in the groups I and III. It is formed by cells in which the cytoplasm is moderately vacuolated, the nuclei deeply stained. The transitional zone is well formed only in the control group. It is formed by cells in which the cytoplasm is eosinophilic and rather dense and the nuclei are situated more closely together than in the zona fasciculata proper. In groups IIA and IIB zona glomerulosa is very small, formed only by two or three layers of cells, the outline between the glomerular and fascicular zones is diffuse and no transitional zone is seen. In groups I and III the thickness of the cortex resembles the control group (fig. 4, 5, 8). In the groups IIA and IIB, on the contrary, the entire cortex is thicker than normal, this thickening having taken place mainly in the fascicular and reticular zones (fig. 6, 7). In the control group and groups I and III the cells of zona fasciculata have a vacuolated cytoplasm which is formed only by a thin eosinophilic network (fig. 12, 13, 16). In groups IIA and IIB the cells of zona fasciculata have a relatively dense cytoplasm which is poor in secretion vacuoles (fig. 14, 15). In all groups the cells of zona reticularis have a rather dense, strongly eosinophilic cytoplasm, in which only some single small vacuoles can be seen. The nuclei are partly vesicular, partly rather deeply stained. In the control group and in the groups I and III the sinusoids are small and almost empty, whereas in the groups IIA and IIB they are relatively large and blood-filled (fig. 17, 18, 19).

*Findings in Spleen.* — The mean weight of the spleen was in different groups as follows: Control group = 754.4 mg; Group I = = 1 201.8 mg; Group IIA = 656.7 mg; Group IIB = 799.0 mg; Group III = 907.6 mg. The spleen thus had gained in weight in the group treated with slowly increasing doses of chlorpromazine. The histological investigation of the spleens revealed no clear changes as compared to the control group: the lymph follicles are well formed in all cases and no pronounced disintegration of the lymphatic tissue is obtained. No significant difference in the structure, amount and distribution of the lymphatic tissue is found between the experimental and control groups. The structure of the reticular tissue seems to be normal and the blood content of the red pulp appears to be considerable.



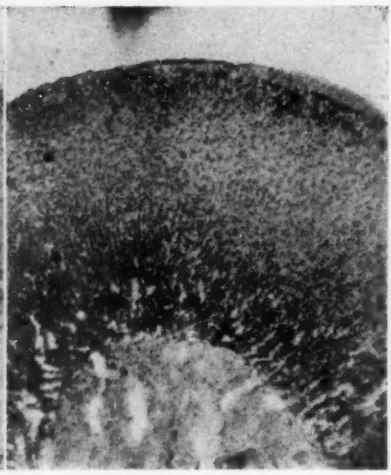
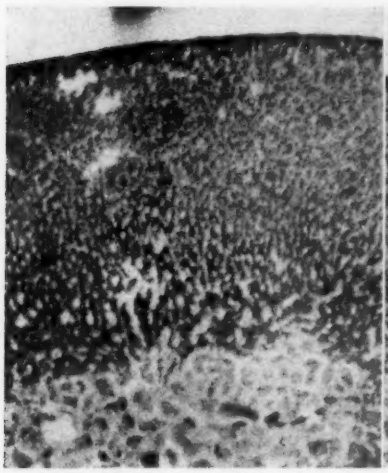


Fig. 4. Fig. 5.

Fig. 4. — Photomicrograph showing the adrenal cortex in the control group. Zona glomerulosa is clearly seen and the transitional zone as a faint grayish line between the zona glomerulosa and fasciculata. 160 ×, haematoxylin-eosin.

Fig 5 — Photomicrograph showing the adrenal cortex in the group treated with slowly increasing doses of chlorpromazine. The glomerular zone is clearly seen. 160×, haematoxylin-eosin.



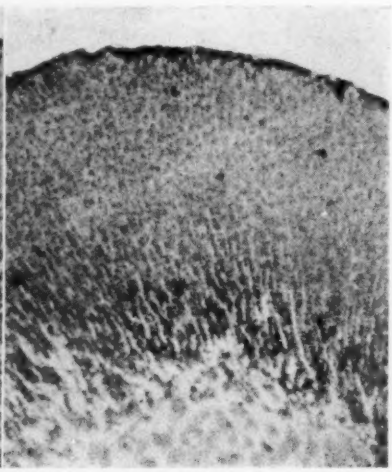


Fig. 6. Fig. 7.

Fig 6. — Photomicrograph showing the adrenal cortex in the group treated with rapidly increasing doses of chlorpromazine. The glomerular zone is very small, the fascicular and reticular zones hypertrophied. 160×, haematoxylin-eosin.

Fig. 7. — Photomicrograph showing the adrenal cortex in the group treated with rapidly increasing doses of chlorpromazine and a small daily dose of ACTH. No essential difference to the preceding group is seen. 160×, haematoxylin-eosin.

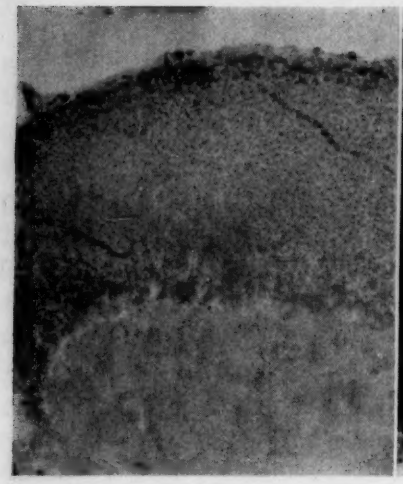


Fig. 8. Fig. 9.

**Fig. 8.** — Photomicrograph showing the adrenal cortex in the group treated with a single and large dose of chlorpromazine. No essential difference is seen to the fig. 4. 160×, haematoxylin-eosin.

**Fig. 9.** — Photomicrograph showing sudanophilia in the adrenal cortex of the control group. The sudanophobic zone is clearly seen. 350×, Sudan III.

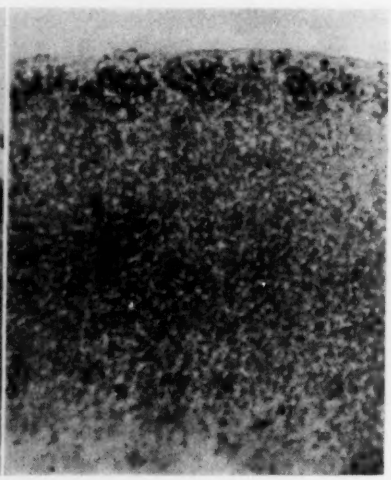


Fig. 10. Fig. 11.

**Fig. 10.** — Photomicrograph showing sudanophilia in the adrenal cortex of the group treated with rapidly increasing doses of chlorpromazine. A diminution of sudanophilic material in zona fasciculata is seen. The sudanophobic zone is lacking. 350 ×, Sudan III.

**Fig. 11.** — Photomicrograph showing sudanophilia in the adrenal cortex of the group treated with rapidly increasing doses of chlorpromazine and a small daily dose of ACTH. No essential difference to the preceding photomicrograph is seen. 350×, Sudan III.

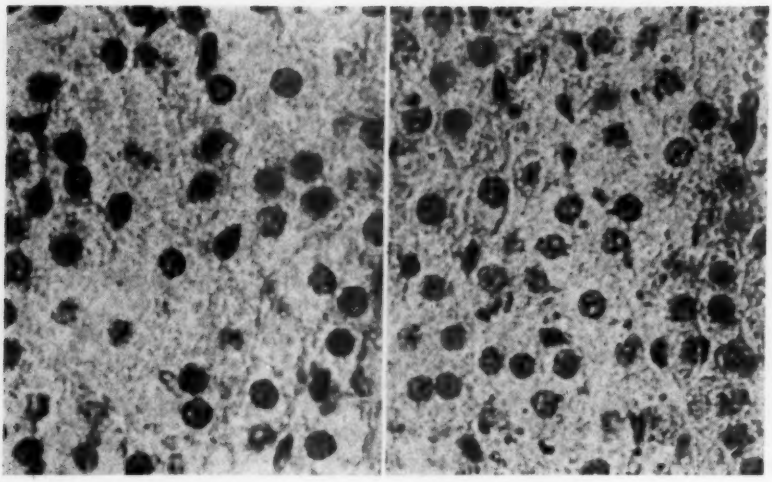


Fig. 12. Fig. 13.

Fig. 12. — Photomicrograph showing cells of zona fasciculata in the control group. A vacuolated cytoplasm is seen. 1800×, haematoxylin-eosin.

Fig. 13. — Photomicrograph showing cells of zona fasciculata in the group treated with slowly increasing doses. A moderately vacuolated cytoplasm is seen. 1800×, haematoxylin-eosin.

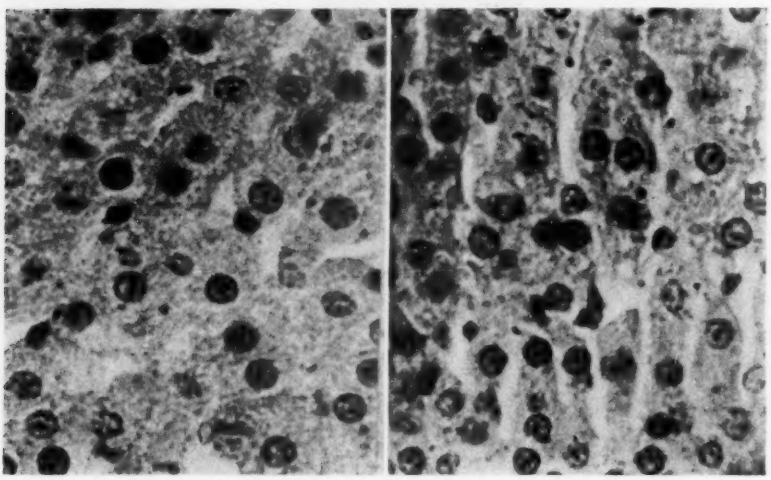


Fig. 14. Fig. 15.

Fig. 14. — Photomicrograph showing cells of zona fasciculata in the group treated with rapidly increasing doses. A relative scantiness of secretion vacuoles in the cytoplasm is seen. 1800×, haematoxylin-eosin.

Fig. 15. — Photomicrograph showing cells of zona fasciculata in the group treated with rapidly increasing doses of chlorpromazine and a small daily dose of ACTH. A relative density of cytoplasm is seen. 1800×, haematoxylin-eosin.

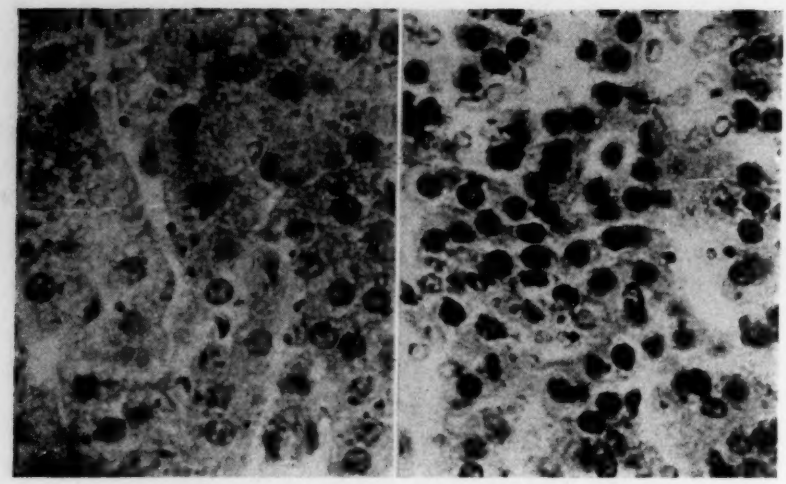


Fig. 16. Fig. 17.

**Fig. 16.** — Photomicrograph showing cells of zona fasciculata in the group treated with a single large dose of chlorpromazine. A moderate vacuolization of the cytoplasm is seen. 1800×, haematoxylin-eosin.

**Fig. 17.** — Photomicrograph showing zona reticularis in the control group. Note the small size of the sinusoids. 1800×, haematoxylin-eosin.

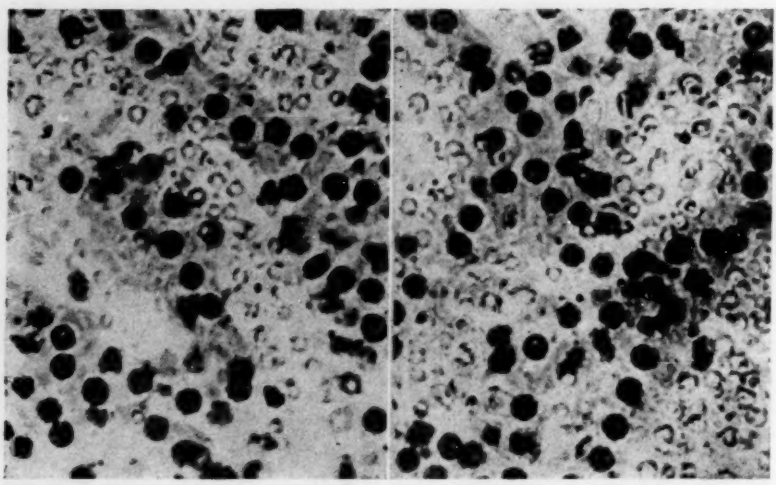


Fig. 18. Fig. 19.

**Fig. 18.** — Photomicrograph showing zona reticularis in the group treated with rapidly increasing doses of chlorpromazine. Note the relatively large size of the sinusoids. 1800×, haematoxylin-eosin.

**Fig. 19.** — Photomicrograph showing zona reticularis in the group treated with rapidly increasing doses of chlorpromazine and a small daily dose of ACTH. The relatively large size of the sinusoids is also here evident. 1800 ×, haematoxylin-eosin.

In the groups I and IIA, treated with progressively increased doses of chlorpromazine, it could, however, be observed a tendency to an inverted correlation between the weights of the adrenals and the spleen. This is illustrated by the fig. 3. It shows that the rats with a small spleen usually have big suprarenals and vice versa.

## DISCUSSION

As is known, the adrenals and the various elements of the hemopoietic system are those organs in which morphologic changes after exposure to non-specific stress most clearly become evident. These organs have a central position in the defense reactions of the organism. According to Selye's general adaptation syndrome, systemic defense reactions are effected through hormonal and nervous responses. As regards the hormonal defense the anterior pituitary is stimulated during stress and so an increased amount of ACTH is produced. The adrenal cortex is stimulated to produce increased amounts of corticoids which in turn increase the resistance to a variety of non-specific stressors. The alarm reaction phase is characterized by the loss of lipid granules from the cortex and hypertrophy of the cortical cells, and the stage of resistance by increased total width of the cortex, increased number and sudanophilia of lipid granules and hypertrophy of the cortical cells. The stage of exhaustion is characterized by extensive cytolytic phenomena and otherwise similar changes than the alarm reaction (8, 43). Typical changes induced in the adrenal cortex by experimental ACTH administration are a diminution of the sudanophil materials and hypertrophy, zona fasciculata, in particular, becoming enlarged (15, 25, 29, 48). Similar morphological and histochemical findings are made by postmortem examination of patients died under ACTH treatment (46). The changes obtained in the adrenal cortex during stress and during experimental ACTH administration thus are similar in many respects. The most striking feature in the reaction of the hemopoietic system is disintegration of the lymphatic elements. At the same time the reticuloendothelial cells of this system are stimulated to phagocytic activity, the cells are hypertrophied and the debris of the disintegrated lymphatic cells are seen partly free in the reticulum, partly in phagocytes.

As we now consider our results in the light of these data we see that the changes seen in the adrenals can be well explained by the presumption that chlorpromazine has acted as a non-specific stressor. In the group treated with slowly increasing doses the condition of the animals had progrediated from the stage of resistance somewhat towards the stage of exhaustion, as can be seen by the finding that their weight had begun to decrease more rapidly. The general condition of the animals, however, was fairly good, the weight of the adrenals was not significantly increased, the lipid content of the cortical cells was considerable and as an indication of increased discharge no transitional zone was seen. The groups treated with rapidly increasing doses of chlorpromazine were characterized by a considerable increase of the weight of the adrenals. The entire cortex was hypertrophied and the discharge phase of the cortical cells was increased as was indicated by the observation that the lipid content of the cells was very low and no transitional zone was seen in any case. A further indication of increased secretory activity was the abundance of sinusoids in the zona reticularis. The poor general condition of the rats and these microscopical findings indicate that they apparently were in the phase of exhaustion. The accessory application of small doses of ACTH had no essential effect to the findings. This is in accordance with the observation expressed by Selye that an administration of anterior pituitary or adrenal cortical hormones does not in essential degree increase the resistance of the experimental animal to non-specific stress (40). The abundance of sinusoids in these groups indicates that the transfer of endogenic secretion products to the blood stream had increased. This finding is similar to that seen during experimental ACTH administration.

With respect to zonation and lipid content of the cortex the group treated with a single and large dose of chlorpromazine closely resembled normal, yet mild changes in the direction of the stage of resistance were seen. The mean weight of the adrenals was almost the same as in the control group. The stress-producing effect of chlorpromazine thus had not clearly manifested itself in this group. Obviously the stress-producing effect of chlorpromazine is due to its central action. This had not have time enough to become manifest in this group.

The morphological findings discussed above, which were interpreted as an evidence to the presumption that chlorpromazine in prolonged use with large doses had acted as non-specific stressor, are in accordance with the previous observations that chlorpromazine in large doses aggravates the effect of other non-specific stressors.

As regards the spleen the findings do not fit to the scheme of the general adaptation syndrome. No cytolytic phenomena or activation of the reticulo-endothelial cells could be seen. On the contrary, the histological picture of the spleen proved to be normal in all groups. The cause of this finding still remains unclear. Presumably the specific effects of chlorpromazine here have inhibited the manifestation of the stress. The paradoxal gain of the weight of the spleen in the group treated with slowly increasing doses apparently could be put in connexion with the peripheral sympathico-parasympathicolytic effect of chlorpromazine which causes an increased hyperemia in the viscera. The observed inverted correlation between the weights of the spleen and the suprarenals possibly indicates a masked tendency to a decrease of the weight of the spleen by the progression of the stress.

## SUMMARY

The effect of large doses of chlorpromazine on the adrenal cortex was studied by 36 male rats and 10 controls. Attention was paid to the appearance of signs of stress.

10 rats were treated with slowly increasing doses of chlorpromazine (increased by 5 mg/kg body weight daily) until the general condition of the animals revealed signs of impairment. Then, after 20 days of treatment the animals were killed. 19 rats were treated with rapidly increasing doses (increased by 25 mg/kg body weight daily). The general condition and the weight of the animals began to go down from the very beginning of the medication. The animals were killed in the state of deep exhaustion after 12—13 days treatment. To 9 rats in this group small accessory doses of ACTH were given (2 IU/kg body weight daily).

In the group treated with slowly increasing doses the weight of the adrenals had not significantly increased, in the group treated with rapidly increasing doses the weight of the adrenals had increased considerably. The microscopical investigation of the adrenal cortex revealed signs which are characteristic to the histological appearance of stress in this organ. These signs were more pronounced in the latter group. The accessory application of ACTH had no essential significance to the results.

7 rats were treated with one very large injection of chlorpromazine (600 mg/kg body weight) and killed 2 hours later. No clear signs of stress could be seen in this group.

The histological picture of the spleen proved to be normal and no clear decrease of weight could be seen. However, in the groups treated with progressively increasing doses of chlorpromazine the weight of the spleen was usually the smaller the bigger the weight of the adrenals. The absence of decrease of weight of the spleen was put in connexion with the increased hyperemia of the viscera which is a consequence of the peripheral mode of action of chlorpromazine.

The results show that chlorpromazine in prolonged use with large doses acts as a non-specific stressor to the organism.

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